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Formulation And *In Vitro* Characterization Of Aceclofenac Sustained Release Pellets Prepared By Suspension Layering Technique Using Sugar Spheres

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Abstract

The present work deals with the aceclofenac pellets prepared by suspension layering technique, using sugar spheres with various concentrations of ethyl cellulose and kollicoat SR-30D as enteric coating materials. Prepared pellets were evaluated for physical characteristics which showed excellent flow properties. Formulation F8 with the maximum drug content of 97.17% showed a prolonged *in vitro* drug release till 10hr when compared with the pure drug. The optimized formulation showed particle size distribution of 546µm.Further stability studies performed according to the ICH guidelines also showed no change in the drug content and property during the shelf life of 3months at prescribed RH and temperature conditions.

Keywords: Aceclofenac, suspension layering, enteric coating, pellets.

Introduction

The delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. To obey this concept sustained drug delivery is one of the routes to reduce the dose frequency and side effects [1]. From a pharmaceutical practical view, various categories of polymers are currently present [2]. So, sustain release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery [3]. Among the different approaches for sustained delivery of drugs pellets has drawn more attention since they are spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm in size for pharmaceutical applications. They are formed as a result of a pelletization process which is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units [4].

The advantages for pellets are, it permits the combination of different release rates of the same drug in a single dosage form , controlled release technology , invariably maximize drug absorption, less susceptible to dose dumping and it can be used for masking the taste of bitter drugs [5,6,7].

In the present work suspension layer method is chosen to formulate the aceclofenac pellets. Solution or suspension layering involves the deposition of successive layers of solution and/or suspensions of drug substances and binder over the starter non-peril seeds, which is an inert material or crystals or granules of the same drug. In fact the coating process is applicable to solution or suspension [5]. The coating pans, fluidized beds, centrifugal granulators, Wurster coaters have been used successively to manufacture pellets by this method [8].

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is a phenyl aceticacid derivative [9], non-steroidal anti-inflammatory drug (NSAID) with wider therapeutic use viz., treatment of various conditions like ankylosing spondylitis [10, 11], rheumatoid arthritis [12] osteoarthritis [13]. It has less gastrointestinal complications [14]. Aceclofenac has daily dose of 200 mg divided in to two doses to maintain the plasma concentration. The short biological half-life about 4 hr and dosing frequency more than one per day with low aqueous solubility and as a consequence, has low oral bioavailability [15] makes aceclofenac an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of aceclofenac is desirable [16, 17].

In the present research work suspension layer method was adopted to coat the aceclofenac pellets using different polymers ethylcellulose, kollicoat SR-30D and HPMCK-4m.

Materials and methods

Materials

Aceclofenac was provided by the Dynamed Pharmaceuticals, Hyderabad. Sugar spheres were purchased from the signet chemical corporation pvt Ltd, Mumbai. HPMCK-4m and ethyl cellulose were purchased from the Dow chemicals, Chennai. Kollicoat SR30D was provided by BASF pharma, Mumbai. All other materials and reagents were of analytical grade.

Drug-Excipients compatibility study

The compatibility study of drug and excipients was done by using fourier transform infrared spectroscopy (FTIR). The FT-IR studies for drug, ethylcellulose, kollicoat Sr-30D drug+ethycelluclose, drug+kollicatSR-30D, drug+mixture of excipients were performed. The method used was drug mixed with KBr (100 times more amount than drug) and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The compressed disc was placed in the light path and the spectrum was obtained.

Method of preparation

Preparation of Drug-Containing Pellets

Aceclofenac loaded pellets were prepared by layering a drug-binder solution (10 % w/w) on to sugar spheres using a fluidized bed coater. Dispersion of aceclofenac and polyvinyl pyrollidone (PVP K - 30) was sprayed using the bottom spray mode. Layered beads were dried at 40ºC for 5– 10 min. The procedure was carried out in 3steps.

Step-1: Drug coating

1. Preparation of coating solution:

PVP K-30 was dissolved in Isopropyl alcohol, aceclofenac was dissolved in PVP K- 30solution. Talc was added to the above solution. A white milky solution was obtained, which was then passed through # 100 Sieve is called as primary solution.

2. Primary coating on spheres

Sugar spheres were loaded in to fluidized bed drier [20] and coat the primary suspension to sugar spheres. The drug loaded pellets were collected.

Step-2: Seal coating /barrier coating [21].

Preparation of barrier coating solution

HPMCK-4m was dissolved in water on continuous stirring to prepare barrier coating solution.

Coating of barrier solution:

The collected pellets were loaded in to fluidized bed drier and coated with the above prepared solution by bottom spray mode [22].

Step-3: Enteric coating [21]

Preparation of enteric coating solution

The non aqueous solution of different polymeric concentrations ethyl cellulose and kollicoat SR 30 D i.e., in 3%,6%,9%,12%concentrations were prepared separately. The solution was plasticized with tri ethyl citrate (10 wt%, based on the mass of the polymer). The non aqueous solvents contain the iso-propyl alcohol (IPA). These are enteric coating solutions.

Coating of enteric coating solution

From the step -2 barrier coated pellets were taken and loaded in to fluidized bed drier. Then by using above enteric coated solution was sprayed on pellets and the pellets dried at 40ºc for 10min. repeat the same procedure for different concentrations of prepared enteric coated solution.

Totally 9 formulations were prepared and individual formula composition was given in table 4.

Evaluation of formulated aceclofenac pellets

Determination of bulk density and tapped density

An accurately weighted quantity of the powder (W) was carefully poured into the granulated cylinder and the volume (V_o) was measured. Then the graduated cylinder was closed with lid and set into the density determination apparatus (bulk density apparatus) which was set for 500 taps,750 taps , and 1250 taps. After that the volume (V_f) was measured and continued the operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulas.

Bulk Density – W/Vo

Tapped Density- W/Vf

Where W- Weight of the powder

V_o - Initial volume (s)

V_f - Final volume.

Hausner's ratio

It indicates the flow properties of the powder and measured by the ratio of Tapped density to bulk density. The standard limits of hausner's ratio given in table 3.

Hausner's ratio= Tapped density /Bulk density.

Carr's index

The compressibility of powder was determined by Carr's compressibility index. The standard limits of carr's index was given in table 2

$$\text{Carr's index} = \frac{Tappeddensity - bulkdensity}{Tappeddensity} * 100$$

Angle of repose

The angle of repose of aceclofenac pellets were determined as follows The powder is allowed to fall over a paper on a horizontal surface through a funnel or an orifice kept at a certain convenient height a cylindrical tube open at both the ends is placed on a paper on a horizontal surface. The powder is then, poured in to the cylinder and the tube is gradually withdrawn without any shaking movements allowing the powder to from a heap on the horizontal surface. The height of heap formed and then the circumference of the base of the heap is drawn on the paper with the help of pencil. The radius of circle obtained is measured. The standard limit values were given table 1.

$\tan\theta = h/r$

h=height of heap

r=radius of the base of the heap

Particle size distribution

This practice was done for the pellets obtained after functional coating to check average size of the pellets. 30g of the pellets were passed through series of sieves was placed (#16, #22, # 25 and #30). The machine was run for 5 minutes, all the sieves were taken out and retained granules were collected by respective sieve and the % retention of pellets by that sieve was calculated. Average particle size was determined. The results were shown in table 7.

Friability test

Friability is the loss of weight of pellets in the container/package, due to removal of fine particles from the surface. Roche Friabilator was used to measure the friability of the pellets. It was rotated at a rate of 25 rpm. 5 g pellets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the pellets were exposed to rolling, resulting from free fall of pellets within the chamber of the friabilator. After 100 rotations (4 min), the pellets were taken out from the friabilator and intact pellets were again weighed. Permitted percentage friability limit is 0.8%. The percent friability was determined using the following formula.

$$\text{Percent friability} = \frac{(W1 - W2)}{W1} \times 100$$

Where W1 = weight of the pellets before test. W2 = weight of the pellets after test.

Drug content estimation

Weighed the pellets equivalent to 100 mg was crushed in mortar and transferred to 100 ml flask. The powder was dissolved in 3 ml of methanol and volume was made up with 3% SLS in pH 6.8 phosphate buffer. The sample was mixed for 5 minutes, then it was filtered through Whatman filter paper. The filtered solution after appropriate dilution (1 ml to 10 ml) with 3% SLS in pH 6.8 phosphate buffer were analyzed by validated UV spectrophotometric method at λ_{max} 275nm.

In Vitro dissolution studies

The dissolution study was carried out using USP test apparatus – II(paddle type in pH 6.8 phosphate buffer along with 3%SLS as media to justify the dissolution media to mimic the gastric intestinal media [27]. In this study, the pellets were placed in the dissolution medium (900 ml) with stirring speed set as 75 rpm. Samples (5 ml) with drawn at a time interval of 0.25, 0.50, 0.75, 1, 2, 4, 8, 10 hours. The samples were withdrawn at predetermined time intervals were subsequently replaced with fresh media. Sample solutions were then filtered through 0.45µm membrane filters and the drug concentration was analyzed spectrophotometrically at 275nm.The percentage drug release was plotted against time to determine the release profile.

Stability Studies

Optimised formulation were packed and stored in ICH certified stability chambers maintained at
25 C and 60% RH
40 C and 75% RH for three months.

Scanning electron microscopy for the optimised formulation

Morphological characterisation of the pellets was studied by the scanning electron micrograph in (JEOL JSM Model 5200).cross-sectional view were obtained by cutting the pellets with a razor blade. The samples were coated to 200 A^0 thickness with gold-platinum using (placo model 3 sputter coater) prior to microscopy working distance of 20nm.a tilt of 0^0 and acclerating voltage of 15 kv were the operating parameters. Photographs were taken within range of 20-500 magnification.

Results and discussion

Drug-excipients compatibility study

The possible interactions for drug and excipients were investigated by FT-IR spectroscopy. The results reveals that there is no appearance or disappearance of peaks which shows that the interaction between the drug and excipients were nil. Thus the compatibility of the drug and excipients was satisfactory.

Flow properties of aceclofenac pellets

The flow properties like bulk density, tapped density, carr's index, hausner's ratio, angle of repose were evaluated for prepared pellets. The bulk density and tapped density of 9 formulations were in the range of 0.8035±0.0021 to 0.8276±0.0014 and 0.8476±0.0021 to 0.8858±0.0018. The carr's index for all the formulations <10% shows excellent flow property. The hausner's ratio were in the range of 1.0477±0.0034 to 1.0927 ±0.0023, the angle of repose for F1 to F8 shows excellent flow property and F9 shows a good flow. The results for all batches were shown in table 5. Almost all the formulations show an excellent flow property.

Friability

The friability of the pellets were tested by using roche friabilator, the values were found to be below 0.4%, which shows that the pellets have desirable hardness. Friability (%) of all the batches is shown in table 6. From the table the formulation which showed least deviation from the standard was taken as the optimized formulation.

Drug content

The drug content of prepared pellets were found to be in the range of 95.50±0.034 to 97.61±0.08 for all the formulations. The formulation (F8) shows the maximum drug content hence this was taken as the optimized formulation. The drug content of all formulations was given in table 6.

In-vitro studies

The in-vitro study of aceclofenac was carried out in USP type-II (paddle) apparatus in pH=6.8 phosphate buffer at 37±0.5°c with stirring speed 75rpm.The in-vitro release was carried out for all the prepared pellets and compared with the pure drug. The pure drug aceclofenac shows the 40.23% release 3hr.The pellets coated with ethyl cellulose i.e.,F4 released the maximum of 87.23±0.34 at 10hr where as F2released 93.31±0.34 at 6hr, F3 released 92.23±0.34 at 8hr ,F5 showed a release of 85.51±0.47 at 10 hr and then no further release was observed from the above formulations. Coming to pellets prepared with kollicoat SR-30D shows the maximum release for F8 with 96.43±0.46 at 10 hrs, other formulations viz., F6 shows 92.21±0.24 at 6hr, F7 shows 90.21± 0.55 at 8hrs, F9 released a maximum of 87.41±0.35 at 10hr.From the results of in-vitro study F8 formulation was taken as the optimized among the other pellets since maximum release was observed upto 10hr. The results were shown in figure 1 and table 8(a) &8(b).

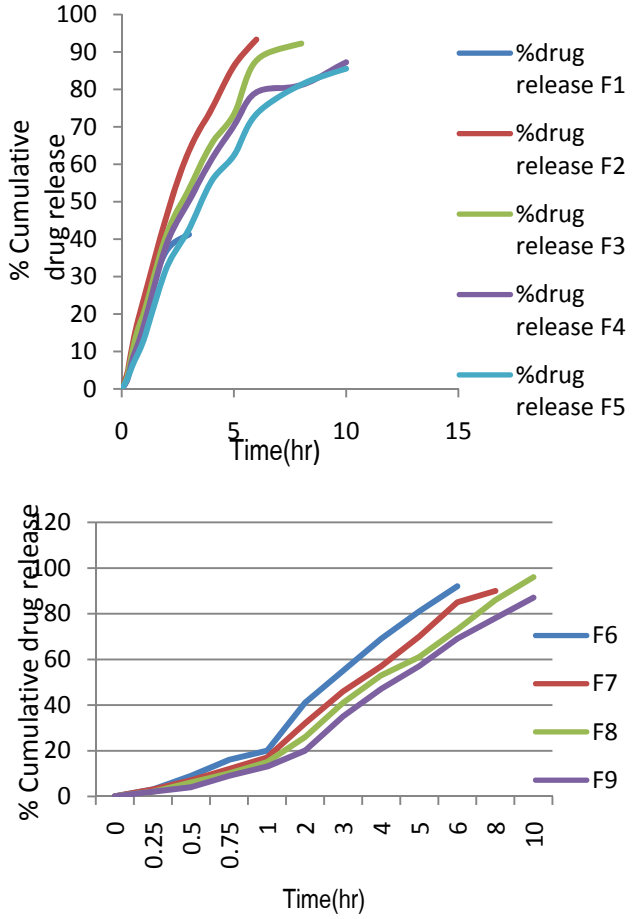


Figure 1: In-vitro profile for Aceclofenac pellets with various concentration of a) ethyl cellulose and b) Kollicoat SR-30D.

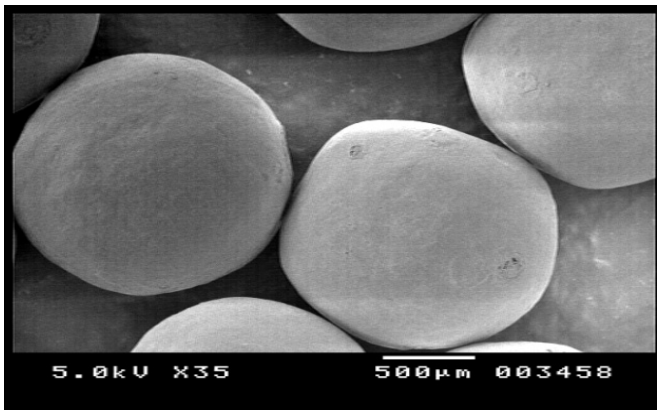
Though all the formulations resulted in similar fashion of release and flow characteristics for convenient purpose formulation F8 was taken for the particle size analysis and morphological studie

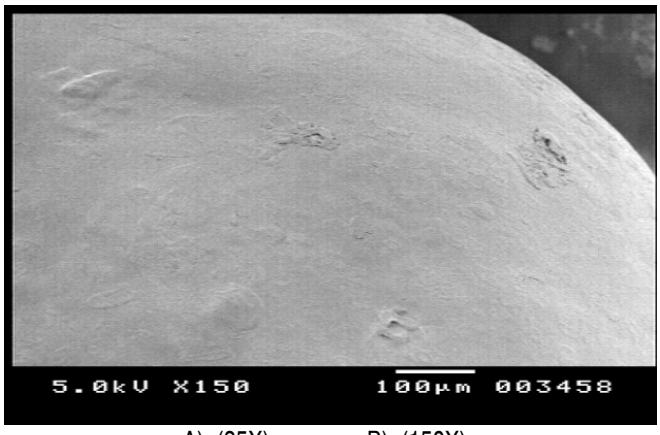
Particle size analysis

Sieve analysis was carried out for the formulation F8. From the result it was evident that most of the pellets were retained in sieve#20. The average diameter of pellet was found to be as 545.6µm.

Scanning electron microscope

The surface morphology of optimized formulation was studied from SEM. It was evident that all
formulated pellets were spherical in shape with uniform size shown at low magnification, the more information about the surface characteristics of optimized pellets were obtained with increasing the magnification. The figure 2 with magnification at 150X shows the external morphology of kollicoat-SR30D shows more rough surface which is due to the density of the matrix and it justifies sustained action. The SEM micrographs were shown in figure 2.





A) (35X) B) (150X)

Figure 2: SEM micrograph for optimized formulation at various magnifications.

Table 1: Standard limits for Angle of repose

Angle of repose	Flow property
< 25º	Excellent
25-30º	Good
30-40º	Average(addition of 0.2% Glident)
>40º	Poor

Table 2: Standard limit for carr's index

Type of flow	Limit
Excellent	<10
Good	11 – 15
Fair	16 – 20
Passable	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

Table 3: Standard limit for Hausner's ratio

Type of flow	Limit
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 -1.34
Very poor	1.35 -1.45
Very very poor	>1.60

Table 4: Composition for formulation of Aceclofenac pellets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug layering Sugar spheres(20-25mesh)	200	200	200	200	200	200	200	200	200
Aceclofenac (mg)	200	200	200	200	200	200	200	200	200
PVP K-30 (mg)	75	75	75	75	75	75	75	75	75
Barrier coating HPMC K-4M(mg)	30	30	30	30	30	30	30	30	30
Enteric coating Ethyl Cellulose (%)	-	3%	6%	9%	12%	-	-	-	-
Kollicoat SR 30 D(%)	-	-	-	-	-	3%	6%	9%	12%
Triethyl citrate(mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Isopropyl alcohol	Qs	qs	qs	qs	Qs	qs	qs	qs	qs
Talc (mg)	8	8	8	8	8	8	8	8	8

Table 5: physico chemical properties of Aceclofenac pellets

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of Repose (θ)	Carr's index (%)	Hausner's ratio
F1	0.8158±0.0009	0.8830±0.0012	24.524±0.011	7.610±0.0011	1.080±0.0061
F2	0.8276±0.0014	0.8807±0.0012	25.236±0.012	5.310±0.0009	1.064±0.0054
F3	0.8045±0.0012	0.8691±0.0006	22.127±0.030	7.432±0.0013	1.080±0.0033
F4	0.8035±0.0021	0.8720±0.0017	26.567±0.030	7.855±0.0016	1.085±0.0045
F5	0.8270±0.0014	0.8676±0.0017	23.434±0.033	4.679±0.0025	1.0490±0.0066
F6	0.7973±0.0016	0.8633±0.0016	25.913±0.026	7.645±0.0036	1.0827±0.0081
F7	0.8106±0.0008	0.8858±0.0018	24.127±0.056	8.489±0.0043	1.0927±0.0023
F8	0.8178±0.0005	0.8820±0.0023	23.974±0.043	7.278±0.0035	1.0785±0.0013
F9	0.8090±0.0018	0.8476±0.0021	26.654±0.034	4.554±0.0043	1.0477±0.0034

All values are expressed as mean ±S.D, n=3.

Table 6: Friability and drug content results of Aceclofenac pellet

Formulation code	Friability (%)	Drug content
F1	0.34±0.0332	96.6±0.08
F2	0.34±0.0523	96.59±0.043
F3	0.39±0.1312	95.50±0.034
F4	0.36±0.1023	97.44±0.25
F5	0.39±0.0645	96.04±0.04
F6	0.34±0.1932	97.61±0.08
F7	0.37±0.0523	96.37±0.04
F8	0.38±0.0644	97.17±0.023
F9	0.39±0.0434	96.27±0.04

All values are expressed as mean ±S.D, n=3.

Table 7: Sieve analysis of optimized formulation (F8)

Sieve no	Nominal mesh aperture size(μm)	Aperture (passed/Retained)	Mean size opening(μm)	Weight powder under size	%Weight retained under smaller sieve	Weight size Nxd
16	1000	1000/pan	1000	0	0	0
20	710	710/1000	855	1	1	855
25	600	600/710	655	7	7	4585
30	500	500/600	550	89.5	89.5	49125
					(n) =100	(nd)= 54665

Table8 (a): In-vitro profile data of Aceclofenac pellets formulation with various concentrations of ethylcellulose

Time (hrs)	%Cumulative release (Mean ±S.D)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.25	2.33±0.38	4.11±0.23	3.21±0.58	2.35±0.36	2.56±0.55
0.5	10.54±0.65	12.26±0.35	10.57±0.65	8.24±0.64	6.54±0.35
0.75	16.25±0.43	18.81±0.47	16.43±0.67	12.25±0.43	9.68±0.35
1	22.34±0.35	24.23±0.23	20.34±0.35	17.12±0.35	13.35±0.31
2	34.62±0.38	46.23±0.24	41.24±0.32	38.54±0.34	32.24±0.35
3	42.35±0.51	63.65±0.24	53.35±0.45	50.21±0.45	42.46±0.54
4	-	74.65±0.24	65.43±0.35	61.22±0.24	55.43±0.35
5	-	86.24±0.24	73.32±0.24	70.22±0.35	62.33±0.41
6	-	93.31±0.34	87.71±0.33	79.21±0.57	73.36±0.43
8	-	-	92.23±0.34	81.11±0.57	81.24±0.35
10	-	-	-	87.23±0.34	85.51±0.47

All values are expressed as mean ±S.D, n=6.

Table 8(b): In-vitro profile data of Aceclofenac pellets formulation with various concentrations of and kollicoatSR-30D.

TIME (hrs)	%cumulative release (Mean ±S.D)			
	F6	F7	F8	F9
0	0	0	0	0
0.25	3.91±0.23	3.21±0.45	2.65±0.45	2.11±0.22
0.5	9.24±0.65	7.22±0.54	6.14±0.16	4.15±0.55
0.75	16.45±0.87	12.45±0.65	10.45±0.65	9.26±0.24
1	20.43±0.24	17.24±0.35	15.23±0.35	13.31±0.34
2	41.24±0.47	32.45±0.35	26.21±0.34	20.43±0.47
3	55.21±0.35	46.34±0.45	41.21±0.45	35.43±0.45
4	69.21±0.57	57.11±0.21	53.55±0.46	47.23±0.46
5	81.56±0.65	70.45±0.46	61.13±0.57	57.25±0.35
6	92.21±0.24	85.25±0.24	72.16±0.45	69.33±0.76
8	-	90.21±0.55	86.21±0.54	78.22±0.21
10	-	-	96.43±0.46	87.41±0.35

All values are expressed as mean ±S.D, n=6

Stability studies

The stability studies were carried out according to the ICH guidelines for the optimized formulation at 25 C/60%±5% RH, and 40 C /75%±5% RH. The colour, shape, diameter and friability were white and spherical with the values 546.65µm, 0.36% respectively, after 3months study at their respective temperature and humidity. The drug content was found to be 96.19% at 6months study, initial it was 96.25%, after 1month 96.34%,3months 96.24% for 25 C/60%±5% RH and the drug content was found to be as 95.90% after 3 months, initially 96.26% 1month 96.21%, 3months96.19%. The pellets maintained the similar property throughout the period. The *in vitro* data conducted for the optimized formulation after stability study the release pattern does not show more variation in results. This indicates that the prepared pellets (F8) are stable at accelerated storage conditions and are suitable for *in vivo* studies in animal models.

Conclusion

The present investigation was focused on the improvement of absorption and oral bioavailability of aceclofenac along with sustained action. To meet the above criteria sustained release pellets of aceclofenac were formulated with hydrophobic rate controlling polymers such as Ethylcellulose and Kollicoat SR-30D as key excipients.

The hydrophobic polymers selected were more reliable as they released the drug slowly, extending it over a long period of time. Alternating concentrations of Kollicoat SR30D had a significant influence on the release profile of the drug. The *in vitro* dissolution profiles of F8 were found to be better formulation. Therefore, it may

be concluded that the sustained release formulations using suspension coating of aceclofenac on sugar spherules are suitable as sustained delivery to meet the pharmacological action for which it is intended. Further studies on the pellets to assure the behavior of release in *in vivo* would be a better approach.

Author's contribution

Contributes this valuable direction and supervision for the research work and support during the literature review.
Contributes for the formulation and evaluation studies present of the research work.
Contributes the supporting to the work and compiling the work.

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